IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PAR PHARMACEUTICAL, INC. and ENDO PAR INNOVATION COMPANY, LLC Plaintiffs, v. ZYDUS PHARMACEUTICALS (USA) INC. and ZYDUS LIFESCIENCES LTD. Defendants.	Civil Action No. _____

DECLARATION OF DAVID DODDS, PH.D. IN SUPPORT OF PLAINTIFFS' MOTION FOR A TEMPORARY RESTRAINING ORDER, PRELIMINARY INJUNCTION, AND EXPEDITED DISCOVERY

David R. Dodds, of full age, hereby declares as follows:

1. I am the founder and President of Dodds & Associates LLC, a consulting company that has been advising start-ups and established companies in the pharmaceutical, renewable/bio-based chemicals, and industrial biotechnology industries since 2002.

Background and Experience

2. I am a chemist trained in organic chemistry, biochemistry, and molecular biology, with a Ph.D. in organic synthesis and post-doctoral work in molecular biology. I obtained a Bachelor of Science degree in biochemistry from the University of Toronto, Trinity College in 1977, a master's degree in biological chemistry from the University of Toronto in 1979, and a Ph.D. degree in organic synthesis from the University of Toronto in 1984. I then served as a Post-Doctoral Fellow in Molecular Biology at the University of Colorado, Boulder until 1986, on behalf of the Medical Research Council of Canada.

3. Over the past 35 years, I have performed worked in both academic and industrial settings for many companies, ranging from small start-up biotechnology companies to major pharmaceutical and industrial companies, including experience in process development and scale-up for the manufacture of active pharmaceutical ingredients ("API") and other synthetic and biological substances in both situations, mainly for companies in the pharmaceutical, fine chemical, and renewable chemical industries. My curriculum vitae, attached hereto as Exhibit A includes a list of my many patents and publications.

4. At all three of my former employers (Sepracor, Schering-Plough, and Bristol-Myers Squibb), I was in charge of the company's efforts to discover and develop processes using combinations of biological and chemical methods and to scale them to provide clinical material. At Sepracor, for instance, I oversaw the company's efforts to use enzymes to produce intermediates for the fine chemical and pharmaceutical industries. In this position, I was responsible, among other things, for writing patent applications for inventions involving the use of enzymes as catalysts in chemical reactions leading to chiral products. At both Schering-Plough and Bristol-Myers Squibb, I was also in charge of the creation and development of chemical processes catalyzed by enzymes to produce chiral intermediates for the companies' products. As enzymes for the necessary reactions were not generally commercially available, we frequently used whole-cell fermentations to perform reactions, and then had to develop processes for the extraction and purification of the desired product from a complex aqueous biological milieu, with attendant degradation reactions that had to be avoided or mitigated. At Bristol-Myers Squibb, by way of further example, solid phase extraction was used during an active fermentation to avoid product inhibition and toxicity issues and increase production of the fermentation. Consideration of the resin to be used, its capacity in the process, and the method

by which the product was eventually eluted from the resin and purified, were all part of this project.

5. As a chemist working in the development of practical processes, the ultimate goal is to create processes by which a commercial material can be made with the lowest expense in all resources (time, raw material, amount of capital equipment occupied, personnel and money) while also producing a product that meets the purity, and more importantly, the impurity specifications, required under Good Manufacturing Processes ("GMP"), including ensuring compliance with any applicable current Good Manufacturing Practice ("cGMP") regulations published by the United States Food and Drug Administration ("FDA") or others. The inconvenience of apparently simple steps that do not work at scale because the physical characteristics of the subject material have not been properly developed, *e.g.*, a filtration step that worked well at bench scale but causes the filter to "blind" or clog very quickly in the pilot plant, or simple extraction steps that form emulsions at scale, is something with which I and the groups I've directed have experience.

6. At both Schering-Plough and Bristol-Myers Squibb, I was directly responsible for coordinating the progression of drug candidates from Drug Discovery to Development, and did this in coordination with personnel in the Drug Discovery group.

7. In my current role as an independent consultant, I continue to advise clients undertaking process development using both chemical and biological methods to produce commercially useful compounds in the pharmaceutical and fine chemical industries, and more recently, in the area of renewable commodity chemicals. This has ranged from total syntheses of pharmaceutical compounds, with all impurity issues, to completely biological processes, which

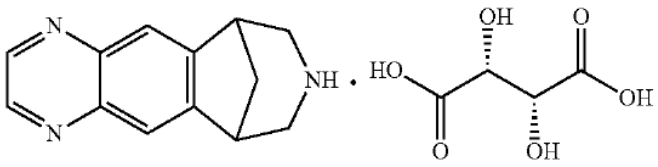
have fallen out of the required specification due to new impurities occurring in a long-practiced fermentation.

Patent-in-Suit

8. I understand that in this lawsuit, plaintiffs Par Pharmaceutical, Inc. and Endo Par Innovation Company, LLC (collectively "Par") accuse Zydus Pharmaceuticals (USA) Inc. ("Zydus USA") and Zydus Lifesciences Ltd. ("Zydus Lifesciences") (collectively "Zydus") of infringing United States Patent No. 11,717,524 ("the '524 patent") (Ex. 1).[1]

9. Broadly speaking, the '524 patent is directed to methods of manufacturing tablets with varenicline tartrate as the API (active ingredient) with low levels of nitrosamine impurities.

10. As described in the patent, varenicline tartrate is a synthetic drug that can be used to treat nicotine dependency, addiction, and withdrawal. '524 patent at 1:15-25. It has the following chemical formula:



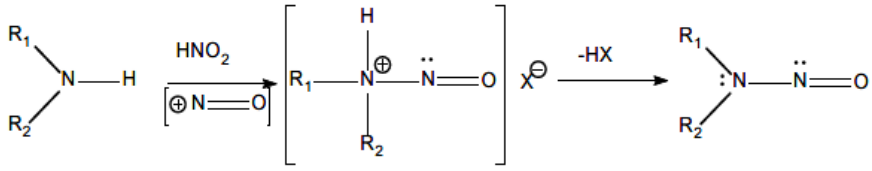
Id. at 1:26-33. Pfizer marketed varenicline tartrate tablets under the trade name CHANTIX® as a partial agonist selective for certain subtypes of nicotinic receptors and indicated for smoking cessation. *Id.* at 1:50-53. However, Pfizer withdrew CHANTIX® from the market due to the presence of unacceptably high levels of nitrosamine impurities. *Id.* at 1:53-55.

11. Nitrosamines are a class of compounds that the FDA has determined to be potentially carcinogenic, and which were found to be present at unacceptably high levels in a

[1] References herein to "Ex. __" refer to the corresponding Exhibit attached to the Declaration of Robert Rhoad being filed herewith.

number of pharmaceutical drug products beginning in approximately 2018. *See, e.g.,* "Control of Nitrosamine Impurities in Human Drugs", Guidance for Industry, U.S. Food and Drug Administration Center for Drug Evaluation and Research (Feb. 2021, Rev. 1) (Ex. 2). As described in that FDA guidance, nitrosamine impurities have a chemical structure in which a nitroso group is bonded to an amine ($R^1N(-R^2)-N=O$), which can form by a nitrosating reaction between amines and nitrous acid, as shown in the following figure:

Figure 1. Representative Reaction to Form Nitrosamines



Id., at 3-4 and Figure 1.

12. Upon learning of the presence of nitrosamines in those pharmaceutical drug products, the FDA and other international regulators undertook an analysis of these impurities in the affected APIs and drug products and investigated the potential root causes of their presence in those products. *Id.* at 1-3. From this investigation, in September 2020, the FDA issued an initial draft of a Guidance for Industry for pharmaceutical manufacturers which included recommendations for evaluating the risk for nitrosamine contamination or formation in their APIs and drug products and the establishment of acceptable daily intake limits for particular nitrosamine impurities found in drug products. Subsequently, the FDA updated that guidance in February 2021. *See* Ex. 2.

13. With respect to varenicline in particular, the FDA has set an acceptable daily intake limit for varenicline-related nitrosamine impurities of 37 nanograms, which equates to 18.5 parts per million ("ppm"), per day. *See* Ex. 3.

14. In July 2021, the FDA announced that Pfizer had discovered the presence of varenicline-related nitrosamine impurities at levels above the FDA's acceptable intake limit in commercial lots of CHANTIX® and that, as a result, Pfizer was recalling those lots from warehouses and eventually discontinued sales of CHANTIX®. *See* https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix (Ex. 10); Fed. Reg., Vol. 88, No. 38 at 12384-85. I understand that Pfizer is still no longer selling that product, and the FDA maintains its inclusion in the "Discontinued Drug Product List'' section of the Orange Book S*ee* Fed. Reg., Vol. 88, No. 38 at 12384-85.

15. The '524 patent discloses methods for manufacturing varenicline tartrate API and varenicline tartrate tablets that have nitrosamine impurity levels well below the daily intake limit set by the FDA. In particular, at a high level, the patent describes the synthesis of what it refers to as "crude Stage III-Varenicline Free Base" (*see* Ex. 1 at 13:20-22), which is then subjected to an acid-base treatment as part of "Stage III" of the process, which reduces the nitrosamine impurities therein to very low levels. *See id.* at 12:60-17:18.[2]

16. The crude Stage III-Varenicline Free Base, which has been purified to remove nitrosamines, is then converted into varenicline tartrate, which is in turn then mixed with

[2] A "free base" in this context means a compound with an amine function, that is, a nitrogen atom bonded to one or more carbon atoms (two carbon atoms in the case of varenicline free base) which is capable of forming a salt with an acid, but is present in the form that is not a salt. If the nitrogen atom, which is basic in nature, were found combined with an acid, and thus in the form of a salt, then that nitrogen atom would have combined with a proton from the acid to form a positively charged species, balanced by the negatively charged acid that has given up the proton. In the free base form, the basic nitrogen atom has not accepted a proton from an acid, as no acid is present. Thus, the nitrogen atom is "free" of any acid, and is termed a "free base."

maltodextrin to form a varenicline-maltodextrin premix in "Stage IV" of the process and eventually combined with other excipients and formed into tablets.[3] *See id.* at 17:18-31:3.

17. The data in the '524 patent reflects that Par was able to successfully reduce the nitrosamines in its varenicline tartrate tablets to less than 5 ppm, well below the FDA's acceptable limit of 18.5 ppm. *See* Ex. 1 at Table 23.

18. As shown by independent testing conducted by the FDA, Par's varenicline tartrate tablets have dramatically lower nitrosamine levels than any of the other tested products, including a small fraction of the number of nitrosamines present in Pfizer's CHANTIX® product:

Company (Manufacturer)	Product	Lots Tested	N-nitroso-varenicline level in micrograms/tablet (nanograms/tablet)	N-nitroso-varenicline level in parts per million (ppm)
Pfizer	Chantix (varenicline) 1mg	EA6080, EC9841, EC9847, EC9848, EX2099, DR5086	0.15-0.47 (150-470)	155-474
Par Pharmaceuticals	Varenicline 1 mg	31960807, 31960801	0.003 (3)	3
Apotex	APO-Varenicline Tartrate 1 mg)	TG2183, TG2181, TG2182	0.027-0.044 (27-44)	27-44
Apotex	APO-Varenicline Tartrate 0.5 mg	TG2180, TG2178, TG2179	0.014-0.021 (14-21)	27-42

[3] Varenicline tartrate is a salt resulting from the basic nitrogen atom described above accepting a proton from the tartaric acid and thus becoming positively charged. This is electronically balanced by the tartaric acid molecule that has given up the proton and has itself become negatively charged. The resulting combination of a positively charged species with a negatively charged species is a salt. Thus varenicline free base is just the varenicline molecule itself, in an electronically neutral form, while varenicline tartrate is the combination of varenicline and tartaric acid. This combination of one molecule of varenicline with one molecule of tartaric acid is a fixed combination that exists at a molecular level. Thus, "varenicline" or "varenicline free base" describes a single molecule of varenicline in an electronically neutral form, while "varenicline tartrate" describes a different compound, one in which one molecule of varenicline is intimately associated with one molecule of tartaric acid.

See "Laboratory analysis of varenicline products", FDA Feb. 8, 2022 (Ex. 3).

19. I understand that the Apotex products referenced therein are products that Apotex was selling in Canada, and that the FDA granted Apotex temporary authority to import them into the United States, notwithstanding the fact that they had nitrosamine levels above the FDA's acceptable daily intake, which it withdrew once it had determined that Par could adequately supply the market with varenicline at or below the acceptable intake limit. *See, e.g.,* https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix (Ex. 10).

20. The '524 patent, titled "Varenicline Compound and Process of Manufacture Thereof," issued on August 8, 2023. Ex. 1. All of the claims of the patent recite methods of making varenicline tartrate tablets (independent claims 1 and 18 and dependent claims 2 through 11 and 19 through 25) and/or varenicline tartrate with nitrosamine impurities below specified levels (independent claims 12 and 26 and dependent claims 13 through 17 and 27 through 30).

21. Claim 1, for instance, recites the following:

> 1. A method of making a varenicline tartrate tablet comprising less than 50 ppm of nitrosamine impurities, the method comprising:
> (a) mixing varenicline free base with tartaric acid to form varenicline tartrate
> (b) means for reducing the nitrosamine impurities to less than 50 ppm per tablet as measured by LC-ESI-HRMS Method;
> wherein the means comprises an acid-base treatment.

22. The remaining claims recite one or more combinations of the following limitations:

- Varenicline tartrate (either alone or as part of a tablet): all independent claims, *i.e.*, claims 1, 12, 18, and 26;
- Acid-base treatment to reduce nitrosamine impurities: all independent claims, *i.e.*, claims 1, 12, 18, and 26;
- Specified nitrosamine levels: less than 50 ppm (claims 12, 18, and 26), 30 ppm (claims 15 and 27), 25 ppm (claims 2, 14, and 21), 20 ppm (claim 3), 15 ppm (claims 4, 16, and 29), or 10 ppm (claim 10, 17, 22, and 30);

- Additional manufacturing steps or additional details regarding the manufacturing steps: claims 4, 5-9, 11, 13, 14, 19, 20, and 23-25; and
- An additional excipient in the tablet: claim 28.

Products Accused of Infringement

23. I understand that the products that Par accuses of infringement in this suit are the generic varenicline tartrate tablets ("Zydus Tablets") that Zydus is selling under the authority of its Abbreviated New Drug Application (ANDA) No. 216723 ("Zydus ANDA"), which the FDA's "Drugs@FDA" website indicates was approved by the FDA on June 12, 2023. *See* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=216723 (Ex. 12).

24. A copy of the prescribing information that is provided to patients along with the Zydus Tablets, and the labelling used on the packaging for the tablets, is available from the Zydus website and other publicly-accessible websites ("Zydus Label"). *See* Ex. 7.

25. The Zydus Label states that the Zydus Tablets are manufactured by Zydus Lifesciences in India and distributed in the U.S. by Zydus USA. *See id.* at 38.

26. Information about how Zydus Lifesciences manufactures the tablets will be set forth in the company's internal batch records and in the Chemistry, Manufacturing, and Controls ("CMC") section of the Zydus ANDA on file with the FDA. Information about how the varenicline tartrate API is made will be set forth, at a minimum, in the Drug Master File ("DMF") filed with the FDA for the API and may also be included in the CMC section of the Zydus ANDA.[4]

[4] A Drug Master File A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, and/or articles used in the manufacturing, processing, packaging, and storing of one or more drug substances. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated

27. Zydus may or may not be making the varenicline tartrate API itself. If Zydus is making the varenicline tartrate API in-house, it will have batch records and other documentation of that process. If Zydus is obtaining the API from a third-party supplier, that supplier will have provided Zydus with information regarding the third-party's manufacturing process in order to support Zydus' ANDA. The documentation used to do this will generally be a DMF, filed by the third-party supplier with the FDA and a copy of which the supplier may or may not have given to Zydus. Regardless of exactly what documentation was used, information about the manufacturing process used by either Zydus or a third-party API manufacturer to make the varenicline tartrate in the Zydus Tablets will have been needed to support Zydus' ANDA.

Opinions Regarding Potential Infringement

28. Par has asked me to evaluate whether Zydus (and/or its third-party API supplier if applicable) is using the claimed methods of the '524 patent to make the Zydus Tablets and/or to make the varenicline tartrate API used in those tablets.

29. As is described in more detail below, I have been able to confirm that the tablet-related limitations of '524 patent claims are satisfied by the Zydus Tablets; but because details concerning how the Zydus Tablets and the varenicline tartrate API included in them are made is not publicly available and has not yet been provided by Zydus, I cannot determine with certainty whether Zydus (or any third-party API supplier) is using the specific manufacturing steps of the claims, including in particular the acid-base treatment recited in each of the independent claims.

New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these. A DMF is not approved or disapproved. Technical contents of a DMF are reviewed by the FDA only in connection with its review of an IND, NDA, ANDA, or an Export Application. *See* https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines.

30. Nevertheless, I can say (1) all of the information available to me supports the possibility that Zydus is using the claimed methods, and (2) of the methods for making varenicline tartrate tablets with the low levels of nitrosamine impurities described in the publications cited on the face of the '524 patent, Par's claimed acid-base treatment method is the most practical and therefore most commercially reasonable process, and is the process that I would choose to implement if given the choice.

Claim 1:

31. As I noted above, claim 1 of the '524 patent recites the following:

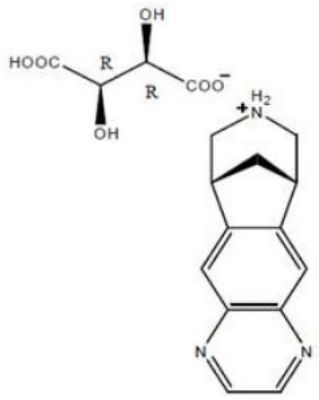
> 1. A method of making a varenicline tartrate tablet comprising less than 50 ppm of nitrosamine impurities, the method comprising:
> mixing varenicline free base with tartaric acid to form varenicline tartrate
> means for reducing the nitrosamine impurities to less than 50 ppm per tablet as measured by LC-ESI-HRMS Method;
> wherein the means comprises an acid-base treatment.

32. The Zydus Tablets are tablets sold in 0.5 mg and 1 mg dosage strengths, and as stated on the Zydus Label, the API in them is, in fact, varenicline tartrate, *see, e.g.*:

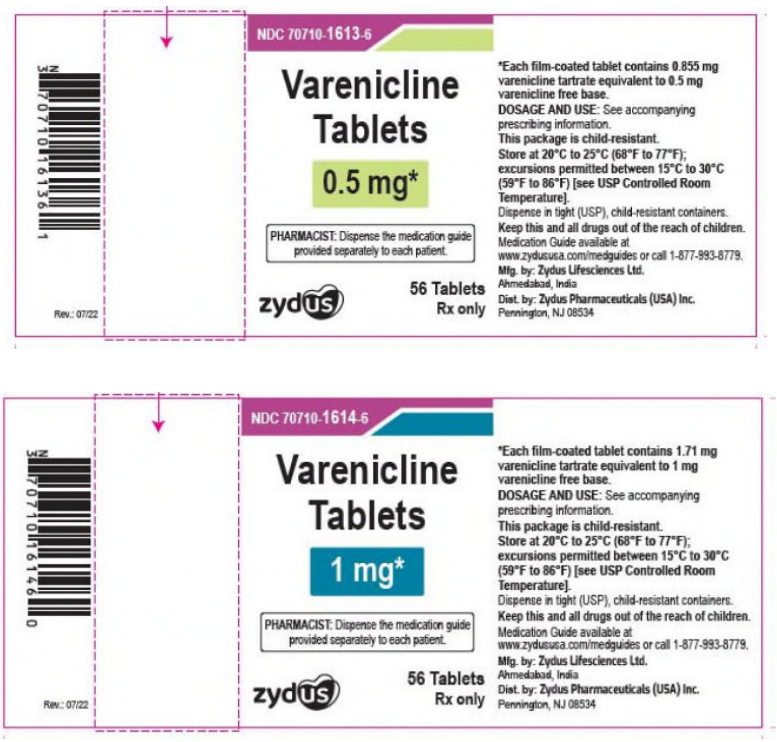
11 DESCRIPTION

Varenicline tablets contain varenicline (as the tartrate salt), which is a partial nicotinic agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a white to off-white to slightly yellow powder with the following chemical name: 7,8,9,10-Tetrahydro-6,10-methano-6*H*-pyrazino[2,3- *h*][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is soluble in water, sparingly soluble in dimethylsulfoxide and slightly soluble in methanol and *N,N*-dimethylformamide. Varenicline tartrate has a molecular weight of 361.35, and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$. The chemical structure is:



* * * *



Ex. 7 To Complaint (Zydus Label) at 17-18, 38-39.

33. As noted above, the FDA's acceptable daily intake limit for varenicline-related nitrosamines equates to 18.5 ppm, and testing conducted by an independent lab (Averica) confirms that the Zydus Tablets have nitrosamine impurity levels below that—specifically, an average of 1.5 ppm for its 0.5 mg tablets (range from 1.3 to 1.6 ppm) and 1.7 ppm for its 1 mg tablets (range from 1.6 to 2.0 ppm). *See* Ex. 13. Thus, the nitrosamine impurity levels in the Zydus Tablets fall within claim 1 of the '524 patent as they have less than 50 ppm of nitrosamine impurities as measured by LC-ESI-HRMS Method (the method used by Averica to test the Zydus Tablets).

34. The remaining limitations of claim 1 recite specifics concerning the method used to make the tablets and API—*i.e.*, (a) "mixing varenicline free base with tartaric acid to form varenicline tartrate," and (b) "means for reducing the nitrosamine impurities to less than 50 ppm

per tablet as measured by LC-ESI-HRMS Method, wherein the means comprises an acid-base treatment."

35. As is noted above, information that would answer the question whether Zydus (and/or any third-party API supplier) are performing those steps would be contained in the applicable DMF and/or in the CMC section of the Zydus ANDA. The FDA maintains a list of DMFs on file with the agency, which is updated quarterly and is available at https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs. There are 17 DMFs included on that list for varenicline tartrate, but Zydus is not listed as the holder for any of those DMFs. Accordingly, it is not clear which one is the DMF for the varenicline tartrate API included in the Zydus Tablets. But, even if we knew that information, the relevant portions of the DMF are maintained by the FDA on a confidential basis and not available except by permission of the holder of the DMF. Likewise, the CMC sections of the Zydus ANDA, which would either show the process used by Zydus or indicate if there were a DMF used to support the Zydus ANDA, are also maintained by the FDA on a confidential basis and not publicly available.

36. I have searched for any publicly available information about how the Zydus Tablets and API are made, but have not found any information specific to Zydus beyond the Zydus Label. Further, I understand that Par's counsel has requested this information from Zydus but that, to date, Zydus has not provided it.

37. Nevertheless, in the absence of having access to the relevant portions of the DMF and CMC section of the Zydus ANDA, I can make the following opinions regarding the Zydus varenicline tartrate product, with respect to the two manufacturing-specific limitations recited in claim 1 of the '524 patent.

38. With respect to the step of "mixing varenicline free base with tartaric acid to form varenicline tartrate," although one could theoretically form varenicline tartrate in some other manner, mixing the free base form of a drug with an acid is by far the most common, the easiest, and most practical way to make the salt form of a drug substance, such as varenicline. Accordingly, in my opinion, it is highly likely that Zydus (or its third-party manufacturer) is forming the varenicline tartrate contained in the Zydus Tablets in this manner.

39. With respect to use of an "acid-base treatment" as a "means for reducing for reducing the nitrosamine impurities to less than 50 ppm per tablet," I have evaluated the treatments disclosed in the Zydus Label, '524 patent, and the other publications listed on the face page of the '524 patent, and the results of independent testing conducted by Averica. I have also reviewed the method disclosed in Wei, *et al.*, WO2021259396 for manufacturing varenicline tartrate tablets with nitrosamine impurity levels low enough to meet the FDA's acceptable daily intake limit ("Wei Method"),

40. Based on that evaluation and my knowledge and experience concerning the manufacturing of FDA-approved drug products and API, I can make the following observations as to whether Zydus and/or any third-party API supplier is using the claimed acid-base treatment to reduce the nitrosamine impurity level below 50 ppm.

41. All of the information available to me supports the possibility that the varenicline tartrate tables manufactured by Zydus are made using varenicline tartrate that has been produced using an acid/base treatment.

42. Further, the '524 patent describes an alternate method for reducing nitrosamine levels in varenicline tartrate tablets, which involves treatment with hydrogen over a palladium catalyst as described in Example 21 of the patent (Ex. 1 at 67:26-41). However, the use of a

hydrogenation method would require that the operation be performed in a hydrogenation suite or similar contained area using equipment dedicated to hydrogenation reactions, that the catalyst be removed and recovered following the reduction operation, and that a palladium metal specification for the API and the final drug product be provided. These three points make the use of a hydrogenation method for reducing nitrosamine impurities less operationally desirable in terms of complexity, resource use, and cost than the use of an acid-base treatment.

43. The Wei reference is the only publication listed on the face of the '524 patent that describes another alternate method for manufacturing varenicline tartrate tablets with nitrosamine levels low enough to satisfy the FDA's daily intake limit. And, as with the hydrogenation method, the claimed acid-base treatment method of the '524 patent is a far more practical and certain method for reducing nitrosamine levels in varenicline tartrate tablets than the Wei method. This is because the Wei reference describes a method called "trituration" in the chemical industry. Trituration is performed by dispersing a solid material (in the case of the Wei reference, this material is varenicline tartrate) in a fluid that is a very poor solvent for the material that one wishes to purify, but is a very good solvent for the impurities which one wishes to remove. By mechanically agitating the solid material dispersed in the fluid (the word "beating" is used in the translation provided for the Wei reference) for some reasonably long period of time, the impurities can be selectively dissolved, and thus removed by collecting the remaining, desired solid material in a filter. The weakness of trituration method is this: the nitrosamine impurities in the varenicline tartrate that are said to be removed in the Wei reference are already present at a relatively low level (but above the level required by the FDA). Thus, the nitrosamine impurities can occur in the starting solid material (the unpurified varenicline tartrate) as very small particles completely surrounded by the varenicline tartrate, and thus will not be

exposed to the trituration solvent, such that those impurities would not be dissolved and removed. To overcome this limitation, the original solid material (the varenicline tartrate) will need to be ground to extremely small particle sizes in order to expose any nitrosamine impurities that would otherwise be completely surrounded by varenicline tartrate. This level of particle size reduction can be accomplished, but will likely cause a dust hazard in the plant. More practically, such fine particle sizes will make the necessary filtration to recover the desired, purified varenicline tartrate difficult.

44. Accordingly, while I cannot determine with certainty whether Zydus and/or any third-party API supplier are using the claimed acid-base treatment to reduce nitrosamine impurity levels without access to the applicable DMF and CMC section of the Zydus ANDA (or other comparable information), in my opinion, it is certainly possible that the acid-base treatment described by Par in the '524 patent is being used. Further, if I were given the choice between using Par's claimed method, the hydrogenation method described in Example 21 of the '524 patent, and the method described in the Wei reference, I would use the claimed method and thus avoid the problems noted above regarding the hydrogenation method and Wei method.

Other Independent Claims – Claims 12, 18, and 26):

45. The other independent claims, besides claim 1, are claims 12, 18, and 26. Each of those claims recite a method of making either varenicline tartrate (claims 12 and 26) or varenicline tartrate tablets (claim 18), and in each instance, as in claim 1, the claims recite that there be less than 50 ppm of nitrosamine impurities and recite mixing varenicline free base with tartaric acid to form varenicline tartrate and the use of an acid-base treatment to reduce or remove those impurities.

46. Accordingly, my opinions with respect to possible infringement by Zydus of claim 1 apply with equal force to these other independent claims.

Dependent Claims 2, 3, 4, 10, 14, 15, 16, 17, 21, 22, 27, 29, and 30:

47. Many of the dependent claims require lower levels of nitrosamine impurities than the independent claims—specifically, less than 30 ppm (claims 15 and 27), 25 ppm (claims 2, 14, and 21), 20 ppm (claim 3), 15 ppm (claims 4, 16, and 29), and 10 ppm (claim 10, 17, 22, and 30). As is noted above, the results of independent testing done by Averica show that the Zydus Tablets have average nitrosamine impurity levels of 1.5 ppm for its 0.5 mg tablets and 1.7 ppm for its 1 mg tablets. Accordingly, the Zydus Tablets satisfy the additional nitrosamine impurity limitation recited in each of those claims.

I declare, under the penalty of perjury, that the foregoing statements made by me are true to the best of my knowledge, information, and belief.

Dated: August 8, 2023

David R. Dodds